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Reliability of Frozen Section Diagnosis of Gallbladder Tumor for Detecting Carcinoma and Depth of Its Invasion

KOJI YAMAGUCHI, MD,[1]* KAZUO CHIJIIWA, MD,[1] SHUJI SAIKI, MD,[1] SHUJI SHIMIZU, MD,[1]
MASAZUMI TSUNEYOSHI, MD,[2] AND MASAO TANAKA, MD[1]
[1]*Department of Surgery I, Kyushu University Faculty of Medicine, Fukuoka, Japan*
[2]*Department of Pathology II, Kyushu University Faculty of Medicine, Fukuoka, Japan*

Background: An accurate frozen section diagnosis is important when deciding the surgical strategy against a gallbladder tumor intraoperatively. Little has been reported on the accuracy of frozen section diagnosis of the gallbladder.

Patients and Methods: In a total of 86 consecutive patients with gallbladder tumor, the accuracy of the frozen section diagnosis was examined. There were 32 patients with polypoid lesions and 54 with nonpolypoid tumors.

Results: The frozen tissue diagnosis and final diagnosis were identical in 82 of the 86 cases, that is, benign in 65 and malignant in 17. The other four cases had different diagnoses, that is, conversion from benign to malignant in two and from malignant to benign in two. The overall accuracy of frozen diagnosis was 95.3% (97.0% for benign and 94.7% for malignant). In 32 polypoid lesions, the accuracy of frozen section diagnosis was 91% (93% for benign; 89% for malignant). In 54 nonpolypoid lesions, the accuracy of diagnosis was 98% (100% for benign; 93% for malignant). The diagnosis of depth of invasion was identical only in 7 (70%) of the 10 carcinoma cases examined, while it was diverse in the remaining 3, that is, conversion from adenocarcinoma invading the subserosa to that limiting to the mucosa in one, from carcinoma within the mucosa to that infiltrating the muscle coat in one, and from carcinoma affecting the muscle layer to that invading the subserosa in the other. Alterations of frozen section diagnosis about being benign or malignant and about the depth of invasion were encountered in seven patients, five of whom had a polypoid tumor.

Conclusions: The intraoperative frozen tissue diagnosis is fairly reliable as to whether lesions are malignant or benign; however, accuracy is low in patients with polypoid lesions of the gallbladder. Also, frozen section diagnosis does not reliably measure the depth of invasion of gallbladder carcinoma. *J. Surg. Oncol. 1997;65:132–136.*

KEY WORDS: **frozen section; gallbladder neoplasms; gallbladder polyp**

INTRODUCTION

Unsuspected and suspected gallbladder carcinoma is an old and new problem for biliary surgeons [1,2]. The recent progress in laparoscopic cholecystectomy provides a wider choice of treatment. Surgical strategy for gallbladder carcinoma, depending on the depth of invasion, has been proposed and accepted [3–5]. One of the final decisions concerning the surgical strategy of unsus-

*Correspondence to: Koji Yamaguchi, MD, Department of Surgery I, Kyushu University Faculty of Medicine, 3-1-1 Maidashi, Higashi-Ku, Fukuoka 812-82, Japan. Fax: (81)92-632-2478.
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pected and suspected gallbladder carcinoma is based on an intraoperative frozen section examination for malignancy and the depth of invasion. If the frozen section diagnosis is reliable, the surgeons can convert the initial operation to further radical operation during the surgery. If the diagnosis is unreliable, the surgeons must wait for the final diagnosis after formalin fixation. Little has been reported on the accuracy of frozen section diagnosis of the gallbladder. We previously reported the clinical problems following laparoscopic cholecystectomy for gallbladder carcinoma, one of them being abdominal wall seeding of cancer cells [3]. In this communication, the accuracy of frozen section diagnosis was reevaluated in patients with polypoid and nonpolypoid tumors of the gallbladder which were suggestive of carcinoma preoperatively.

PATIENTS AND METHODS

This series was composed of 86 consecutive Japanese patients who had intraoperative frozen section diagnosis of the gallbladder from January 1982 to December 1995 in Department of Surgery I, Kyushu University Hospital, Fukuoka, Japan. The frozen section diagnoses and final permanent diagnoses were performed by three surgical pathologists. Clinical records were reviewed in these 86 patients. There were 43 men and 43 women and their age ranged from 30 to 83 years with a mean of 56.5 years. Thirty-two patients had polypoid lesions and 54 patients had nonpolypoid tumor-like lesions of the gallbladder. A congenital choledochal cyst was present in two patients and sarcoidosis in two. All the lesions were suggestive of gallbladder carcinoma from clinical and/or imaging findings and hence, intraoperative frozen section examination was performed to make a definite diagnosis and to decide the surgical strategy. Intraoperative and final histopathologic diagnoses were reviewed depending on the macroscopic type of the gallbladder tumors, that is, polypoid and nonpolypoid tumor-like lesions. The depth of invasion of gallbladder carcinoma was presented as follows: m, limited to the mucosa; pm, infiltrating the muscle coat; ss, invading the subserosal layer.

In 67 patients whose intraoperative frozen section diagnosis was benign, all underwent cholecystectomy. In the remaining 19 patients whose frozen section diagnosis was malignant, cholecystectomy was done in 8 patients, extended cholecystectomy in 10, and external biliary drainage in 1. Two patients who had undergone simple cholecystectomy had a liver bed resection and a bile duct resection and lymph node dissection added on the 12th and 31st postoperative days, respectively, because the final diagnosis of the depth of invasion of adenocarcinoma was changed from pm to ss in one patient and from hyperplastic polyp to ss in another.

TABLE I. Total Accuracy of Frozen Section Diagnosis and Accuracy of Frozen Section Diagnosis of Benign Disease and Malignant Disease

	Total accuracy (%)	Benign disease (%)	Malignant disease (%)
Polypoid lesion	90.6	92.6	80.0
Nonpolypoid tumor-like lesion	98.1	100	92.9
Total	95.3	97.0	94.7

RESULTS

Polypoid Lesions of the Gallbladder

Thirty-two of 86 patients who underwent a frozen section examination presented with polypoid tumors of the gallbladder. The frozen section diagnosis and the final diagnosis were identical in 29 of the 32 patients, but were different in the remaining 3 patients. The frozen section diagnosis was benign in 27 patients and malignant in 5. In these five patients with malignant diagnosis, the final diagnosis was also malignant in four and benign in one (conversion from adenocarcinoma [m] to adenoma). In those 27 patients with a benign diagnosis, the final diagnosis was benign in 25 and malignant in 2. In those two malignancies, a hyperplastic polyp was converted to an adenocarcinoma (ss) and an adenoma was changed to an adenocarcinoma (m). The total accuracy of frozen section diagnosis was 90.6% (29/32), with the accuracy of diagnosing benign tumors 92.6% (25/27) and of diagnosing malignant tumors 80.0% (4/5) (Table I). The final diagnoses of all 32 patients with polypoid lesions were cholesterol polyps in 13, hyperplastic polyps in 1, inflammatory polyps in 1, polyps (nonspecific) in 1, adenomyoma in 1, chronic cholecystitis in 5, adenoma in 4, and adenocarcinoma in 6 (Table II).

Nonpolypoid Tumor-Like Lesions of the Gallbladder

A total of 54 patients with nonpolypoid tumor-like lesions of the gallbladder had participated in intraoperative frozen section examination. Of the 54 patients, intraoperative diagnosis was benign in 40 and malignant in 14. In the former 40 patients, the final diagnosis was also benign in all. Of the latter 14 patients, the final diagnosis was malignant in 13 and 1 was converted from adenocarcinoma (ss) to chronic cholecystitis with the hyperplastic epithelium extending into the Rokitansky-Aschoff sinuses. The total accuracy of frozen section diagnosis was 98.1% (53/54) with the accuracy of benign diagnosis 100% (40/40), and of malignancy of 92.9% (13/14)(Table I). The final diagnosis of these 54 patients was chronic cholecystitis in 33, xanthogranulomatous cholecystitis in 2, cholesterol polyps in 1, cholesterolosis in 1, adenomyoma in 3, adenoma in 1, and adenocarcinoma in 13 (Table II).

TABLE II. Final Diagnosis of 86 Patients Who Underwent Frozen Section Examination of the Gallbladder

Polypoid lesion (32)		Nonpolypoid tumor-like lesion (54)	
Benign		Benign	
Cholesterol polyp	13	Chronic cholecystitis	33
Chronic cholecystitis	5	Xanthogranulomatous cholecystitis	2
Inflammatory polyp	1	Cholesterolosis	1
Hyperplastic polyp	1	Cholesterol polyp	1
Polyp (nonspecific)	1	Adenomyoma	3
Adenomyoma	1	Adenoma	1
Adenoma	4		
Malignant		Malignant	
Adenocarcinoma	6	Adenocarcinoma	13

Diagnosis of Gallbladder Carcinoma

Of 19 patients whose frozen tissue section diagnosis was adenocarcinoma, the final diagnosis was adenocarcinoma in 17, adenoma in 1, and chronic cholecystitis with hyperplastic epithelium in 1 (Table III). In 2 of the 67 patients whose frozen section diagnosis was benign, the final diagnosis was converted from adenoma to adenocarcinoma (m) and from hyperplastic polyp to adenocarcinoma (ss). In 7 of the 10 patients examined for the depth of invasion, the diagnosis by frozen and permanent sections was the same (m in 5, pm in 1, and ss in 1)(Table IV). In the other three patients, the diagnoses were different, that is, conversion from ss to m in one, from m to pm in one, and from pm to ss in the other. Five of the seven lesions whose frozen section diagnosis was changed by final diagnosis in Table IV were of polypoid configuration. The reason was different estimation of noninvasive atypical epithelium in four (in the Rokitansky-Aschoff sinuses in two) and different cut-surface of the tissue blocks or the different tissue blocks in three.

TABLE III. Alteration of Frozen Section Diagnosis of Benign or Malignant Gallbladder Disease*

Frozen section diagnosis	Final diagnosis
Hyperplastic polyp	Adenocarcinoma (ss)
Adenoma	Adenocarcinoma (m)
Adenocarcinoma (m)	Adenoma
Adenocarcinoma (ss)	Chronic cholecystitis

*m, limited to the mucosa; ss, invading the subserosal layer.

TABLE IV. Diagnosis of Depth of Invasion of Gallbladder Carcinoma*

Frozen diagnosis	Final diagnosis	No. of cases
No change		
m	m	5
pm	pm	1
ss	ss	1
Change		
m	pm	1
pm	ss	1
ss	m	1

*m, limited to the mucosa; pm, infiltrating the muscle coat; ss, invading the subserosal layer.

DISCUSSION

Laparoscopic cholecystectomy was originally indicated for uncomplicated gallbladder stones. With the improvement of instruments and techniques, the indication of laparoscopic cholecystectomy has become broad and it is now applied for complicated cholelithiasis [6–10] and even for tumor or tumor-like lesions of the gallbladder [11–14]. However, the role of laparoscopic cholecystectomy in the treatment of gallbladder tumor is controversial. Some recommended the procedure for a laparoscopic excisional biopsy of the gallbladder [13]. Others proposed that whenever gallbladder carcinoma is suspected, open cholecystectomy should be done [11,12,15–20]. The timing of the second operation is important in gallbladder carcinoma because of the early and rapid recurrence. Some recommended conversion to open laparotomy immediately after frozen section examination [21,22]. Others advocated excision of the port sites immediately after the frozen section and to await the second operation after the paraffin section diagnosis [23,24]. In such circumstances, the reliability of intraoperative frozen section diagnosis is crucial. However, the report on the accuracy of the intraoperative frozen section diagnosis of the gallbladder is limited.

All the 86 patients underwent intraoperative frozen section diagnosis because gallbladder carcinoma was suggested from clinical and imaging features. They presented with polypoid lesions in 32 and nonpolypoid tumor-like lesions in 54 patients. This series also represented gallbladder lesions which mimicked gallbladder carcinoma preoperatively. Polypoid lesions consisted of adenomas, hyperplastic polyps, fibrous polyps, cholesterol polyps, and others [25]. Tumor-like lesions that masquerade as gallbladder carcinoma include adenomyomatous hyperplasia, chronic cholecystitis, and xanthogranulomatous cholecystitis [26,27]. One of the difficulties in frozen section diagnosis is the estimation of the degree of atypia. If the lesion is composed largely of proliferation of atypical epithelium with mild to moderate degree, the diagnosis is adenoma. If the degree of atypia corresponds to that of invasive adenocarcinoma and shows no invasive growth, the diagnosis is noninvasive carcinoma or in situ carcinoma. However, the estimation of the degree of atypia of noninvasive atypical epithelium is difficult, because there is no frank evidence of invasion. Some surgical pathologists may diagnose adenoma with moderate to severe atypia, while others may diagnose the same lesion as noninvasive adenocarcinoma. Also, the presence of Rokitansky-Aschoff si-

nuses is troublesome [28]. The epithelium of mild to moderate atypia lining the Rokitansky-Aschoff sinuses is easily interpreted as adenocarcinoma, especially when the sinuses are located in the muscular layer or in the subserosal area, as shown in 2 of the 86 present cases.

At the time of intraoperative frozen section examination, the section examined is limited in number. In one case, the frozen section diagnosis was a hyperplastic polyp, but the detailed examination after formalin fixation revealed adenocarcinoma invading the subserosa in the same polypoid lesion. The site of examination is important and the detailed examination after formalin fixation is mandatory, even if the frozen section diagnosis is benign.

The accuracy of the diagnosis of adenocarcinoma in frozen section of the polypoid lesions of the gallbladder was lower than that of the tumor-like lesions. This may be because the estimation of noninvasive atypical epithelium depends only on cellular and structural atypia and is more difficult than that of invasive atypical epithelium, as is often shown in the epithelial neoplasm of the colorectum and ampulla of Vater [29]. The diagnosis of adenoma was altered to that of noninvasive adenocarcinoma in one, and noninvasive adenocarcinoma conversely was altered to adenoma in one. In another, hyperplastic epithelium extending along Rokitansky-Aschoff sinuses was overdiagnosed as invasive gallbladder carcinoma invading the subserosa. Immunohistochemical staining of tumor markers [30] or application of molecular biology techniques such as point mutation of codon 12 of the Ki-ras oncogene, mutation of p53, or transcription of topoisomerase mRNA may be an adjuvant useful method.

Depending on the depth of invasion of gallbladder carcinoma, reasonable resection has been proposed by several authors [3–5]. Therefore, the accurate diagnosis of the depth of invasion is important during surgery. If there are no complications, excessive surgery may be justified because the clinical course of gallbladder carcinoma remains dismal even after radical resection [4,5,28]. In contrast, insufficient surgery annoys the surgeons. The frozen section diagnosis of benign disease was converted to the final diagnosis of adenocarcinoma in two cases. In one case, the diagnosis of adenoma was converted to that of adenocarcinoma (m). However, the lesion was noninvasive carcinoma and additional operation was not necessary. In another case, the diagnosis of hyperplastic polyp was converted to adenocarcinoma invading the subserosa. Therefore, additional resection of the bile duct and liver bed and lymph node dissection were performed on the 31st postoperative day. In 7 of 10 patients with gallbladder carcinoma examined by frozen section, the depth of invasion of gallbladder carcinoma was identical to the final diagnosis. In the other three, the diagnosis of the depth of invasion was corrected by final paraffin section diagnosis. Alteration from ss to m was seen in one, from m to pm in one, and from pm to ss in the other. Unnecessary extended cholecystectomy with excision of the extrahepatic bile duct and lymph node dissection was carried out in the first case because of the frozen section diagnosis. Liver bed resection, bile duct resection, and lymph node dissection were added on the 12th postoperative day after cholecystectomy in the third case.

In 1992, Yamaguchi and Tsuneyoshi [1] and Shirai et al. [2] reported that the second operation against inapparent gallbladder carcinoma following the initial open cholecystectomy should be performed according to the depth of invasion of gallbladder carcinoma. The surgical problems concerning suspected or unsuspected gallbladder carcinoma are almost the same at the era of open and laparoscopic cholecystectomies, except for early port-site recurrence of gallbladder carcinoma [15–22,31–44], which is not seen at the era of open cholecystectomy. It is not well known if to excise the trocar sites is enough or not because peritoneal dissemination occurs simultaneously. It seems that the most logical approach in cases where a suspected tumor is operated upon, is to operate through an open approach. The present study showed that frozen section was fairly reliable about the diagnosis of whether the lesion was malignant or benign, but there was some limit to its accuracy about the diagnosis of polypoid lesions of the gallbladder and about the diagnosis of depth of invasion of gallbladder carcinoma. Frozen section examination should be done whenever gallbladder carcinoma is suspected perioperatively. The second operation should be done depending on the depth of invasion of the gallbladder carcinoma as determined by detailed histopathologic examination.

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